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BRUCE LONDA
NORRIS, MCLAUGHLIN & MARCUS, P.A.
220 EAST 42ND STREET, 30TH FLOOR
NEW YORK, NY 10017

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,645	ANKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- *If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.*
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27, 43, 45-50, 53-63, 65-67, 68-70, 72-74, and 76-81* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,17,18,21-23,25-27,46,53-60,69,70,72-74 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: 11-16, 19-20, 24, 43, 45, 47-50, 61-63, 65-68, 76-77 and 79-81

DETAILED ACTION

1. Claims 1-27, 43, 45-50, 53-63, 65-70, 72-74, and 76-81 are pending.

2. Applicant's election with traverse of Group 1, Claims 2-6, 8-10, 17-18, 21-23, 25-27, 45, 54-58, and 69-74 (now claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78) drawn to a method of treating, preventing or ameliorating chronic heart failure or acute heart failure comprising administering a compound to the extend of bile acid that is able to reduce the production, absorption and/or the effect of an endotoxin (LPS), filed 4/26/04, is acknowledged. The traversal is on the grounds that (1) claims directed to the pharmaceutical formulation and method of treating should not be restricted. (2) The applied reference which is actually Matsumori performs experiments in mice using Quabain which is a glycoside and not bile acid. Matsumori does not show data on treating congestive heart failure. (3) To the extent of compound in claim 1 may be a bile acid, it is suggested that the election is actually an election of species that so satisfied the issued restriction. Upon reconsideration, the prior art search has been extend to include LPS binding protein to the extend of BPI. Therefore, the requirement of Group 1 (now claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78) and Groups 2-66 and 68-74 is still deemed proper and is therefore made FINAL.

3. Claims 11-16, 19-20, 24, 43, 45, 47-50, 61-63, 65-68, 76-77 and 79-81 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78, drawn to a method of treating, preventing or ameliorating chronic heart failure or acute heart failure comprising administering a compound wherein the compound is bile acid or LPS binding protein to the extend of BPI that is able to reduce the production, absorption and/or the effect of an endotoxin (LPS), are being acted upon in this Office Action.

5. Claims 46, 53, and 78 are objected to as the claims encompass non-elected embodiments.

6. Claim 10 is objected to because "tile" should have been "the".

7. Claims 3-10, 17-18, 21-23, 25-27, 54-60, 69-70, and 72-74 are objected to because "A" should have been "The" for said dependent claims.

8. Claims 7, 46 and 78 are objected to for reciting non-elected embodiments.

9. Claim 23 is objected to because "claim 21, 22".

10. Claim 53 is objected to because "of an 10 endotoxin".

11. Claim 78 is objected to because "BI" should have been "BPI" and "permeability" should have been "permeability".

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of reducing LPS-mediated increase in TNF and IL6 production in whole blood of patients with cachexia due to liver cirrhosis by administering ursodeoxycholic acid in vitro, and (2) a pharmaceutical composition comprising bile acid for reducing LPS-mediated increase in TNF and IL6 production in whole blood of patients with cachexia due to liver cirrhosis, **does not** reasonably provide enablement for a method of "preventing" chronic heart failure or acute heart failure in any patient comprising administering to the patient any or all "compound", any compound such as bile acid such as any one of ursodesoxycholic acid, chemdeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid that is able to reduce the production, absorption and/or the effect of LPS as set forth in claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of reducing LPS-mediated increase in TNF and IL6 production in vitro using whole blood of patients with cachexia due to liver cirrhosis by administering ursodeoxycholic acid. The specification further discloses endotoxin LPS and TNF alpha are elevated in patients with chronic heart failure (pages 31-32) which can be detected by ELISA (page 35). The specification suggests that ursodeoxycholic acid (UDCA) may be tested in patient with oedema or with cardiac cachexia (page 40). However, no in vivo working example is provided.

The specification does not teach how to make all "compound", and pharmaceutical composition comprising all compound and diuretics, much less for preventing chronic heart failure or acute heart failure because the term "compound" without the chemical structure or amino acid sequence has no function.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is insufficient guidance as to which is undisclosed compound is able to inhibit all response by any cell to endothoxin (LPS), which undisclosed "compound" is able to reduce the permeability of the gut wall to bacteria and/or LPS for the claimed method, which "compound" is able reduce the amount of bacteria and/or free endotoxin (LPS) that is able to translocate from the gut into the circulation of the patient for the claimed method, which "compound" is able to bind to LPS molecule and reduce the available endotoxin in patient and which "compound" from colostrums of human, bovine or other mammalian origin is effective for treating, "preventing" or ameliorating chronic heart failure or acute heart failure in any patient.

Further, the term "prevent" as define by the Webster's II New Riverside University Dictionary as "to keep from happening or to anticipate or counter in advance". The specification fails to provide guidance and working example as how to select or identify an individual before heart failure set in, how to predict who would or would not heart failure, let alone preventing chronic heart failure from happening. Given the indefinite number of undisclosed "compound", it is unpredictable which undisclosed "compound" is effective for treating or ameliorating chronic heart failure, which undisclosed "compound" is effective for "preventing chronic heart failure or acute heart failure.

Even if the pharmaceutical composition is limited to the specific compound such as any one of ursodesoxycholic acid, chemdeoxycholic acid, dehydrocholic acid, cholic acid and deoxycholic acid, there is a lack of in vivo working example demonstrating such compound can treat chronic heart failure or acute heart failure.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

14. Claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* "compound" for a method of treating or preventing or ameliorating chronic heart failure or acute heart failure, (2) all "compound" that is able to inhibit any or all response by any cell to endothoxin (LPS) for a method of treating or preventing or ameliorating chronic heart failure or acute heart failure, all "compound" that is able to decrease all cytokine production by all cell in response to LPS for the claimed method, (3) all "compound" that is able to reduce the

permeability of the gut wall to bacteria and/or LPS for the claimed method, (4) all "compound" that is able reduce the amount of bacteria and/or free endotoxin (LPS) that is able to translocate from the gut into the circulation of the patient for the claimed method, (5) all "compound" and all agent that is able to reduce the permeablility of the gut in patient for the claimed method.

The specification discloses only a method of reducing LPS-mediated increase in TNF and IL6 production in vitro using whole blood of patients with cachexia due to liver cirrhosis by administering ursodeoxycholic acid. The specification further discloses endotoxin LPS and TNF alpha are elevated in patients with chronic heart failure (pages 31-32) which can be detected by ELISA (page 35). The specification suggests that ursodeoxycholic acid (UDCA) may be tested in patient with oedema or with cardiac cachexia (page 40). However, no in vivo working example is provided.

With the exception of the specific ursodesoxycholic acid for a method of reducing LPS-mediated increase in TNF and IL6 production in whole blood of patients with cachexia due to liver cirrhosis by administering ursodeoxycholic acid in vitro, there is insufficient written description about the structure associated with function of all compound for treating, preventing, ameliorating chronic heart failure mentioned above because the term "compound" or "diuretics" without the chemical structure or amino acid sequence has no structure, much less function.

The specification discloses only ursodesoxycholic acid as a method of reducing LPS-mediated increase in TNF and IL6 production in whole blood of patients with cachexia due to liver cirrhosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of compound to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "agent" in claim 22 has no antecedent basis in base claim 1 because the word "agent" is not recited in claim 1.

The "agent" in claim 23 has no antecedent basis in base claim 21 because the word "agent" is not recited in claim 21.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-2, 17-18, 25-26, 53-54, 69-70, 72-73 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Kambayashi *et al* (Internal J Pharmacology 18(6-7): 371-8, June-July 1996; PTO 892).

Kambayashi *et al* teach a method of treating chronic congestive heart failure in a patient by administering a compound such as Vesnarinone that is able to reduce the effect of endotoxin such as LSP stimulated the release of TNF alpha and suppresses IL-6 release by cell such as mononuclear phagocytes (See abstract, in particular). The reference compound is administered orally (See Materials and methods, in particular). Claims 25-26 are included in this rejection because it is within the purview of one skill in the pharmaceutical art to administer intravenously. The reference further teaches the drug is useful in the treatment of diseases such as cachexia involving TNF alpha. Thus, the reference teachings anticipate the claimed invention.

19. Claims 1-2, 17-18, 25-26, 53-54, 69-70, 72-73 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsumori *et al* (Circulation 89(3): 955-8, March 1994; PTO 892).

Matsumori *et al* teach a method of treating chronic congestive heart failure in a human patient by administering a compound such as Vesnarinone that is able to reduce the effect of endotoxin such as LSP stimulated the release of TNF alpha and suppresses IL-6 release by cell such as mononuclear phagocytes (See abstract, in particular). The reference compound is administered orally (See Materials and methods, in particular). Claims 26-27 are included in this

rejection because it is within the purview of one skill in the pharmaceutical art to administer intravenously or rectally. The reference further teaches the drug is useful in the treatment of diseases such as cachexia involving TNF alpha. Thus, the reference teachings anticipate the claimed invention.

20. Claims 53, 57-58, 72-73 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0528312A1 (published Oct 4, 1992; PTO 892).

The EP 0528312A1 patent teaches a pharmaceutical composition comprising bile acid such as rusodeoxycholic acid (See page 5, in particular) and a method of treating a patient with liver cirrhosis or chronic hepatopathologies due to hypercholesterol synthesis (page abstract, page 2, first paragraph, in particular). The reference method inherently ameliorating body wasting or cachexia associated with liver cirrhosis since the properties of bile acid in the reference pharmaceutical composition is the same as that of the claimed pharmaceutical composition. Thus, the reference teachings anticipate the claimed invention.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U,S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1, 3-4, 7-10, 21-23, 27, 46, 53, 55-56, 59-60, 74 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kambayashi *et al* (Internal J Pharmacology 18(6-7): 371-8, June-July 1996; PTO 892) or Matsumori *et al* (Circulation 89(3): 955-8, March 1994; PTO 892) each in view of US Pat No 6,509,317 (filed 1/22/99; PTO 892).

The teachings of Kambayashi *et al* and Matsumori *et al* have been discussed supra.

The invention in claims 3, 8, 55 and 59 differs from the teachings of the references only in that the method wherein the compound is able to bind to LPS.

The invention in claims 4, 56 and 60 differs from the teachings of the references only in that the method wherein the compound is able to reduce the available toxin in the patient.

The invention in claim 9 differs from the teachings of the references only in that the method wherein the compound is able to reduce the absorption of endotoxin by the patient from the gut.

The invention in claim 10 differs from the teachings of the references only in that the method wherein the compound is able to substantially reduce the availability of endotoxin for absorption from the gut such that the amount of endotoxin that is absorbed is reduced or is less biologically active.

The invention in claim 21 differs from the teachings of the references only in that the method wherein the compound is able to reduce the permeability of the gut wall to bacteria and/or endotoxin.

The invention in claim 22 differs from the teachings of the references only in that the method wherein the compound is able to reduce the amount of bacteria or free endotoxin (LPS) that is able to translocate from the gut into the circulation of the patient.

The invention in claim 23 differs from the teachings of the references only in that the method wherein the compound is largely unabsorbed from the gut.

The invention in claim 27 differs from the teachings of the references only in that the method wherein the compound is administered rectally.

The invention in claims 7, 46 and 78 differs from the teachings of the references only in that the pharmaceutical composition wherein the compound is BPI.

The '317 patent teaches a method of treating chronic heart failure by administering a compound that binds to LPS such as bactericidal/permeability-increasing protein (BPI) (See claims 1-10 of '317 patent, col. 3, line 52-54, in particular). The reference compound is administered systemically or topically such as oral, intravenous, intramuscular, subcutaneous and

is readily optimize by those skilled in the art of good medical practice (See col. 9, lines 7-38, in particular). The reference pharmaceutical composition further comprises a second agent(s) such as diuretics (See col. 5, line 35-60, in particular) and the reference method is useful for alleviating the negative physiological effects of endotoxemia associated with chronic heart failure (See col. 6, line 28-33, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Vesnarinone as taught by Kambayashi *et al* or Matsumori *et al* for the LPS binding compound such as BPI as taught by the '317 patent for a method of treating chronic heart failure as taught by Kambayashi *et al*, Matsumori *et al* and the '317 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '317 patent teaches LPS binding compound is effective for treating chronic heart failure by reducing endotoxemia that is associated with elevated level of circulating LPS (See col. 6, line 28-33, claim 6 of '317, in particular). Claims 21-23 are included in this rejection because the '317 patent teaches that increase intestinal permeability of endotoxin during cardiopulmonary bypass and allowing for bacterial translocation and release of endotoxin into the circulation has been well documented (See col. 12, line 56-65, in particular). The administration of the LPS binding protein would obviously enhance the clearance of LPS by reducing the permeability of the gut wall to bacteria and/or endotoxin. Claims 27 and 74 are included in this rejection because it is within the purview of one ordinary skill in the pharmaceutical art to administer the compound rectally and readily optimize by those skilled in the art of art of good medical practice as taught by the '317 patent (see col. 9, lines 7-38, in particular).

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

26. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
June 28, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600